1.3 IN THE CLAIMS:

1. (Currently Amended) A method of promoting natural bypass in a mammal ~~so~~ to provide increased blow flow to tissue served by an occluded or partly occluded vessel, comprising administering to the mammal a mixture of proteins derived from ground bone.

2. (Currently Amended) The method according to claim 1 wherein the mixture of proteins derived from ground bone comprises at least two growth factors selected from the group consisting of bone morphogenic protein-2 (BMP-2), bone morphogenic protein-3 (BMP-3), bone morphogenic protein-4 (BMP-4), bone morphogenic protein-5 (BMP-5), bone morphogenic protein-6 (BMP-6), bone morphogenic protein-7 (BMP-7), transforming growth factor β1 (TGF-β1), transforming growth factor β2 (TGF-β2), transforming growth factor β3 (TGF-β3) and ~~firbroblast~~ fibroblast growth factor 1 (FGF-1).

3. (Original) The method of claim 1, wherein the mammal is a human.

4. (Original) The method of claim 1, wherein the mixture is administered subcutaneously, intramuscularly, or intravenously.

5. (Original) The method of claim 1, wherein the mixture is administered discretely or continuously.

6. (Currently Amended) The method of claim 1, wherein ~~the~~ said mixture further comprises a growth factor selected from the group consisting of insulin-like growth factor-1

(IGF-1), epidermal growth factor (EGF), hepatocyte growth factor (HGF), transforming growth factor α (TGF-α), ~~or~~ and platelet-derived growth factor (PDGF).

7. (Original) The method of claim 1, wherein the mixture further comprises a preservative or an adjuvant.

8. (Currently Amended) ~~The method of claim 1,~~ A method of promoting natural bypass in a mammal to provide increased blow flow to tissue served by an occluded or partly occluded vessel, comprising administering to the mammal a mixture of proteins derived from ground bone, wherein the mixture comprises BMP-2, BMP-3, BMP-7, TGF-β, and FGF.

9. (Currently Amended) ~~The method of claim 1,~~ A method of promoting natural bypass in a mammal to provide increased blow flow to tissue served by an occluded or partly occluded vessel, comprising administering to the mammal a mixture of proteins derived from ground bone, wherein the mixture is derived by:

(i) grinding mammalian bone, to produce ground bone;

(ii) cleaning the ground bone, to produce cleaned ground bone;

(iii) demineralizing the cleaned ground bone, to produce demineralized cleaned ground bone;

(iv) extracting protein from the demineralized cleaned ground bone using a protein denaturant to yield extracted protein;

(v) ultrafiltering the extracted protein to separate out high molecular weight proteins;

(vi) ultrafiltering the extracted protein to separate out low molecular weight proteins;

(vii) transferring the extracted protein to a non-ionic denaturant;

(viii) subjecting the extracted protein to an anion exchange process;

(ix) subjecting the extracted protein to a cation exchange process; and

(x) subjecting the extracted protein to a reverse phase HPLC process.

10. (Original) The method of claim 9, wherein the mammalian bone is bovine bone.

11. (Original) A method of promoting vessel growth to heal a heart artery that has been partly or fully occluded, comprising administering to the heart a mixture of proteins derived from ground bone.

12. (Currently Amended) The method according to claim 11 wherein the mixture of proteins derived from ground bone comprises at least two growth factors selected from the group consisting of bone morphogenic protein-2 (BMP-2), bone morphogenic protein-3 (BMP-3), bone morphogenic protein-4 (BMP-4), bone morphogenic protein-5 (BMP-5), bone morphogenic protein-6 (BMP-6), bone morphogenic protein-7 (BMP-7), transforming growth factor β1 (TGF-β1), transforming growth factor β2 (TGF-β2), transforming growth factor β3 (TGF-β3), and ~~firbroblast~~ fibroblast growth factor 1 (FGF-1)~~,~~.

13. (Original) The method of claim 11, wherein the heart is a human heart.

14. (Original) The method of claim 11, wherein the mixture is administered subcutaneously, intramuscularly, or intravenously.

15. (Original) The method of claim 11, wherein the mixture is administered discretely or continuously.

16. (Currently Amended) The method of claim 11, wherein the mixture further comprises a growth factor selected from the group consisting of insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), hepatocyte growth factor (HGF), transforming growth factor α (TGF-α), ~~or~~ and platelet-derived growth factor (PDGF).

17. (Original) The method of claim 11, wherein the mixture further comprises a preservative or an adjuvant.

18. (Original) The method of claim 11, wherein the mixture comprises BMP-2, BMP-3, BMP-7, TGF-β, and FGF.

19. (Currently Amended) The method of claim 11, wherein ~~the~~ said mixture is ~~derived~~ obtained by:

(i) grinding mammalian bone, to produce ground bone;

(ii) cleaning the ground bone, to produce cleaned ground bone;

(iii) demineralizing the cleaned ground bone, to produce demineralized cleaned ground bone;

(iv) extracting protein from the demineralized cleaned ground bone using a protein denaturant~~;~~ to yield extracted protein;

(v) ultrafiltering the extracted protein to separate out high molecular weight proteins;

(vi) ultrafiltering the extracted protein to separate out low molecular weight proteins;

(vii) transferring the extracted protein to a non-ionic denaturant;

(viii) subjecting the extracted protein to an anion exchange process;

(ix) subjecting the extracted protein to a cation exchange process; and

(x) subjecting the extracted protein to a reverse phase HPLC process.

20. (Original) The method of claim 19, wherein the mammalian bone is bovine bone.

21. (Currently Amended) A method of ~~promoting angiogenesis to assist in recovery from tissue damage comprising,~~ treating ischemic tissue damage in a mammal, said method comprising at least the step of: administering to ~~the~~ said ischemic tissue a composition that comprises a mixture of proteins derived from ground bone.

22. (Currently Amended) The method according to claim 21 wherein the mixture of proteins derived from ground bone comprises at least two growth factors selected from the group consisting of bone morphogenic protein-2 (BMP-2), bone morphogenic protein-3 (BMP-3), bone morphogenic protein-4 (BMP-4), bone morphogenic protein-5 (BMP-5), bone morphogenic protein-6 (BMP-6), bone morphogenic protein-7 (BMP-7), transforming growth factor β1 (TGF-

β1), transforming growth factor β2 (TGF-β2), transforming growth factor β3 (TGF-β3), and ~~firbroblast~~ fibroblast growth factor 1 (FGF-1)~~;~~.

23. (Currently Amended) The method of claim 21, wherein ~~the~~ said ischemic tissue is human tissue.

24. (Currently Amended) The method of claim 21, wherein ~~the mixture~~ said composition is administered subcutaneously, intramuscularly, or intravenously.

25. (Currently Amended) The method of claim 21, wherein ~~the mixture~~ said composition is administered discretely or continuously.

26. (Currently Amended) The method of claim 21, wherein ~~the~~ said mixture further comprises a growth factor selected from the group consisting of insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), hepatocyte growth factor (HGF), transforming growth factor α (TGF-α), ~~or~~ and platelet-derived growth factor (PDGF).

27. (Currently Amended) The method of claim 21, wherein ~~the mixture~~ said composition further comprises a preservative or an adjuvant.

28. (Currently Amended) The method of claim 21, wherein ~~the~~ said mixture comprises BMP-2, BMP-3, BMP-7, TGF-β, and FGF.

29. (Currently Amended) The method of claim 21, wherein ~~the~~ said mixture is ~~derived~~ obtained by:

(i) grinding mammalian bone, to produce ground bone;

(ii) cleaning the ground bone, to produce cleaned ground bone;

(iii) demineralizing the cleaned ground bone, to produce demineralized cleaned ground bone;

(iv) extracting protein from the demineralized cleaned ground bone using a protein denaturant~~;~~ to yield extracted protein;

(v) ultrafiltering the extracted protein to separate out high molecular weight proteins;

(vi) ultrafiltering the extracted protein to separate out low molecular weight proteins;

(vii) transferring the extracted protein to a non-ionic denaturant;

(viii) subjecting the extracted protein to an anion exchange process;

(ix) subjecting the extracted protein to a cation exchange process; and

(x) subjecting the extracted protein to a reverse phase HPLC process.

30. (Original) The method of claim 29, wherein the mammalian bone is bovine bone.

31. (New) The method of claim 21, wherein said bone is mammalian bone.

32. (New) The method of claim 31, wherein said mammalian bone is bovine bone.

2.0 RESPONSE

2.1 STATUS OF THE CLAIMS

Claims 1-30 were pending at the time of the instant Action.

Claims 11 and 18 have been allowed.

Claims 1-2, 6, 9, 12, 16, 19, and 21-29 have been amended herein.

Claims 31 and 32 have been added herein.

Claims 1-32 are now pending in the case.

2.2 SUPPORT FOR THE CLAIMS

Support for each of the claims as amended herein is provided by the Specification, drawings, and original claims as filed; further it is Applicants' belief that no new matter has been introduced as a result of the accompanying amendment.

2.3 SUBSTANCE OF EXAMINER INTERVIEW CONDUCTED IN THE OFFICE JULY 15, 2004

Applicants appreciate the extensive Interview conducted in the Office on July 15, 2004 with Examiner Jeffrey Russel and Applicants' new undersigned representative, Dr. Mark D. Moore, to discuss the pending claims and to address the clarity and prior art issues which remained with respect to certain of the pending claims. As stated on the Interview Summary provided by the Office, during this interview, all claims were discussed, as well as all rejections and prior art. Applicants concur with Examiner Russel's finding that the rejection of claim 24 over Levine *et al.* should be withdrawn, and appreciates the Examiner's suggestion with respect to the clarity issues concerning language in the claims. Applicants and their new representative also appreciate the helpful suggestions of the Examiner to overcome the rejection of certain

claims under Section 103 of the Statutes by limitation of the claimed compositions to exclude bFGF to more properly point out and distinctly claim particular aspects of Applicants' invention.

Mindful of the Applicants' recent change-of-counsel in this application, and in efforts to secure an economically-expedient allowance of the pending claims, Applicants' representative also appreciates the Examiner's availability for the recent interview, and his helpful suggestion of appropriate claim language to provide expedient allowance of the pending claims.

Applicants believe that Examiner Russel will now concur that all pending claims are allowable in view of the prosecution history and in view of the detailed and enabling disclosure of the present specification, particularly in light of the amendment and remarks herein.

2.4 THE OBJECTIONS TO THE DRAWINGS HAVE BEEN OVERCOME.

Re: Item 2 of the Action:

Item 2 of the Action has been addressed by renumbering FIG. 19C and FIG. 19D so that they are now FIG. 19B and FIG. 19C. Applicants appreciate the helpfulness of the Examiner in pointing out this deficiency in the Specification and believe that the Objection is now overcome.

FIG. 13A and FIG. 13B have been amended to correct the spelling of "Sialidase," and FIG. 15A and FIG. 15B have been corrected to include the required sequence identifiers.

Applicants believe this to be a full, complete, and timely response to the Objection to the Drawings, and respectfully request that it be withdrawn in light of the present paper.

2.5 THE OBJECTIONS TO THE SPECIFICATION HAVE BEEN OVERCOME.

Re: Item 3 of the Action:

Item 3 of the Action has been addressed by updating the priority information on page 1, by correction of the text to conform to the drawing corrections provided herein, and by moving text from the footnotes on page 18 to the body of the Specification.

Applicants believe this to be a full, complete, and timely response to the Objection to the Specification, and respectfully request that it be withdrawn in light of the present paper.

2.6 THE OBJECTION TO THE CLAIMS HAS BEEN OVERCOME.

Re: Item 4 of the Action:

The objection to the claims has been overcome by providing correction to the typographical errors identified by the Examiner.

Applicants believe this to be a full, complete, and timely response to the Objection to the Claims, and respectfully request that it be withdrawn in light of the present paper.

2.7 THE REJECTION OF CLAIMS 1, 3-5, 7, 21, 23-25, AND 27 UNDER THE JUDICIALLY-CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING IS MOOT.

Re: Item 5 of the Action:

Claims 1, 3-5, 7, 21, 23-25 and 27 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,211,157.

This rejection has been addressed by providing an appropriately-executed terminal disclaimer in view of the commonly owned priority application, now U.S. Patent 6,211,157.

Applicants believe this to be a full, complete, and timely response to the Rejection, and respectfully request that it be withdrawn in light of the submitted terminal disclaimer, and consideration of the forgoing remarks.

2.8 COMMONLY OWNED U.S. PATENT 6,211,157 IS NOT AVAILABLE AS PRIOR ART. THE REJECTION OF CLAIMS 3-5, 7, 23-25 AND 27 UNDER 35 U. S. C. § 103(A) IS IMPROPER.

Re: Items 6-8 of the Action:

Items 6-8 of the Action have been addressed by providing evidence that the present application and U.S. Patent 6,211,157 were commonly owned at the time the invention was made.

According to MPEP § 706.02(I)(1), "effective November 29, 1999, subject matter which was prior art under former 35 U. S. C. §103 *via* 35 U. S. C. § 102(e) is now disqualified as prior art against the claimed invention if that subject matter the claimed invention 'were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.'" The present application was filed on December 22, 2000, which is after the November 29, 1999 effective date of this Rule. Furthermore, the present application and the 6,211,157 patent were, at the time the present invention was made, owned by the same entity or subject to an obligation of assignment to the same entity, namely Sulzer Biologics, Inc., now Zimmer Orthobiologics, Inc. (copies of the Assignment documents and Change of Name documents are attached herewith as evidence of initial and extant co-ownership of the issued patent and the present application by Zimmer Orthobiologics, Inc. and its predecessor companies). Thus, Applicants respectfully submit that U. S. patent 6,211,157 is not available as prior art in any obviousness determination, and respectfully request that the rejection be withdrawn.

2.9 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 102(A/B) AND § 103(A) IS OVERCOME.

Re: Items 9-11 of the Action:

Claim 21 has been rejected under 35 U. S. C. § 102(a), allegedly as being anticipated by Chinese Patent 1,163,780, while claim 27 has been rejected, allegedly as anticipated, under 35 U. S. C. § 102(b), and claims 23-25 have been rejected as being legally obvious under 35 U. S. C. § 103(a). Applicants respectfully traverse. The priority date of the present application is 10/16/98, and the Action at Item 6 concludes that claim 21 is entitled to such priority. The publication date of the Chinese Patent is November 1997, less than a year before the priority date. Applicants note that a reference cited under 35 U. S. C. § 102(a) may be removed by antedating the reference showing Applicants' invention prior to the availability of such a reference, as provided in C. F. R. § 1.131.

While Applicants reserve the right to provide such a declaration, they believe that this rejection is overcome on the merits alone, as the reference does not teach or suggest "A method of treating ischemic tissue damage in a mammal, said method comprising at least the step of: administering to said ischemic tissue a composition that comprises a mixture of proteins derived from ground bone," as exemplified in pending claim 21. The Action admits on page 6, that the Chinese Patent is said to teach a method of stimulating bone growth and healing, when a growth factor is administered by injection to a bone site. As discussed in the recent Examiner interview, the present Specification notes that the disclosed compositions have usefulness in treating a variety of conditions, included among them, the treatment of ischemic tissue damage (see *e.g.*, the Summary and Detailed Description). As Applicants representative and Examiner Russel discussed, there is no evidence that the cited reference has anything to do with treating ischemic tissue damage, or that the compositions disclosed therein have any usefulness in treating any condition other than promoting bone growth when injected to a bone site. As such, Applicants

believe that the present claims are free from all prior art rejections in view of the Chinese patent, and respectfully request that these rejections be withdrawn.

Item 11 notes that claim 26 is rejected allegedly as being obvious over the Chinese patent in further view of Hunziker ('300). Applicants again respectfully traverse. As stated above, they believe that this rejection is overcome on the merits, as the primary reference neither teaches nor suggests "A method of treating ischemic tissue damage in a mammal, said method comprising at least the step of: administering to said ischemic tissue a composition that comprises a mixture of proteins derived from ground bone," and even in view of the secondary reference of Hunziker does not provide the required expectation of success or motivation to combine the two references as is required by the law.

By application of the obviousness standard held in the case of *In re Vaeck*, 20 U.S.P.Q. 1438 (Fed. Cir. 1991), one must conclude that these two references do not render the claims obvious. It was in this landmark case, where the Federal Circuit stated that in order for an examiner to make out a *prima facie* case of obviousness two things must be shown:

(1) That the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention; and

(2) That the prior art must demonstrate a reasonable expectation of success of the invention.

Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure (emphasis added).

Furthermore, in the case of *In re* Dow Chemical Co. (837 F. 2d 469, 5, U.S.P.Q.2d 1529, Fed. Cir. 1988) the court held that an "obvious-to-experiment" standard is not an acceptable alternative for obviousness, and that there must be a reason or suggestion in the art, *other than* the knowledge learned from the Applicant's disclosure.

In the instant case, however, there is neither the *suggestion* nor the *reasonable expectation of success*. Even if one could somehow postulate that one or more of the cited references might suggest that the claimed method might, in an abstract sense, be *plausible*, there is certainly no teaching or suggestion in either the Chinese patent, or in Hunziker as to how one would go about developing a method for treating ischemic tissue damage in a mammal, or for selecting a composition from ground bone for such as method as is presently claimed. Similarly, there is no suggestion in the cited references, either alone or in combination, that such an approach would be successful. These references either alone or in combination do not provide the motivation or the teaching for either preparing, or using the claimed bone-derived compositions for methods of treating ischemic tissue damage.

Furthermore, Applicants submit that the combination of references relied upon by the Examiner also clearly fails to satisfy the tripartite test of *In re O'Farrell* (7 U. S. P. Q. 2d 1673, 1680, Fed. Cir. 1988). In *O'Farrell*, the Court held that in order for a reference or references to obviate an invention, it must be shown that the reference(s) contain(s):

(1) Detailed enabling methodology for practicing the claimed invention;

(2) A suggestion for modifying the prior art to practice the claimed invention; and

(3) Evidence suggesting that the invention would be successful.

In the present case, neither of the cited references provides any teaching relevant to the question of how one of skill in the arts would be motivated to prepare one or more of the claimed bone-derived compositions, or to use them in one or more of the claimed methods, particularly in any method for treating ischemic tissue damage.

Also in the present case, none of the cited references provides any suggestion for combining the teachings of the Chinese patent and Hunziker *et al.*, or for modifying any of these prior disclosures in a manner that would allow one to arrive at the present invention.

Finally, in the present case, none of the cited obviousness references provides any evidence that the particular compositions of the present invention would be successful in the claimed methods. Clearly the rejection is improper as it fails the tripartite test of *In re O'Farrell.*

Applicants assert that any combination of the cited references is, at best, merely an invitation for further experimentation in the field, and at most, an "obvious-to-try" situation. However, there is *no* reasonable expectation of success, *nor* is there the motivation or teaching to guide a skilled artisan how to achieve such success. The Federal Circuit, in the case of *In re Geiger* (815 F.2d. 686, 2 U.S.P.Q.2d 1276, Fed. Cir. 1987), held that obviousness cannot be established by combining the teachings of the prior art to produce a claimed invention, absent some teaching, suggestion or incentive supporting the combination. Again, Applicants believe that the rejection fails the test of *In re Geiger.*

Further, in *Amgen v. Chugai Pharmaceutical Co. Ltd.*, (927 F. 2d 1200, 18 U.S.P.Q. 2d 1016, 1022, Fed. Cir. 1991) the Court affirmed that obviousness under 35 U. S. C. § 103 is a question of law, and that both the suggestion and the expectation of success must be founded in the prior art, and not in the Applicant's disclosure. Because the suggestion and expectation of success are absent in the cited art, Applicants assert that the rejection also fails the test of *Amgen v. Chugai Pharmaceutical Co. Ltd.*

Therefore, as a matter of both fact and law, the present Applicants believe that the obviousness rejection over the Chinese -780 patent, either alone or in combination with Hunziker *et al.,* is improper and must be withdrawn.

Because the claims in the case particularly point out the distinct features of the inventive methods disclosed in the Specification, and because each of such claims is clearly distinguished

over the previously cited art (either alone or in combination) Applicants believe that, as a matter of fact, and as a matter of law, the rejection advanced under 35 U. S. C. § 103 cannot stand.

Applicants respectfully submit that all aspects of the instant 35 U. S. C. § 103 rejections have been overcome and withdrawal of the rejections is earnestly solicited.

2.10 THE REJECTION OF CLAIMS 21-30 UNDER 35 U. S. C. § 102(B) IS OVERCOME.

Re: Item 12 of the Action:

Item 12 of the Action notes that claims 21-30 have been rejected allegedly as being anticipated by Levine *et al.*. Applicants again respectfully traverse.

As stated above, Applicants believe that this rejection is overcome, as the reference neither teaches nor suggests "A method of treating ischemic tissue damage in a mammal, said method comprising at least the step of: administering to said ischemic tissue a composition that comprises a mixture of proteins derived from ground bone," as provided in independent Claim 21.

As discussed in the recent Examiner interview, the present Specification provides methods and compositions for the treatment of ischemic tissue damage. As Applicants representative and Examiner Russel recently discussed, there is no evidence that Levine et al has anything to do with treating ischemic tissue damage. As the Action notes on pages 7-8, the Levine reference discusses means for inducing bone growth, and for filling in contour defects and reconstructing osseous defects in children. The reference does not provide any suggestion or enabling teaching that the compositions disclosed therein would have any usefulness in treating any condition other than promoting bone growth. As such, Applicants believe that the present claims are free from all prior art rejections in view of the Levine et al., and respectfully request that these rejections be withdrawn.

2.11 THE REJECTION OF CLAIMS 2, 12, AND 22 UNDER 35 U. S. C. § 102(E) MAY BE OVERCOME BY A SUBMISSION UNDER 37 C. F. R. § 1.131.

Re: Item 13 of the Action:

Claims 2, 12, and 22 have been rejected under 35 U. S. C. § 102(e), allegedly as anticipated by Ripamonti et al. (U.S. Pat. Appl. Publ. No. 2003/0104977). Applicants respectfully traverse.

As previously noted, the filing date of the present application is 12/22/00. The publication date of the application to Ripamonti is 6/5/03, with a filing date of 3/31/00, which is less than a year before the filing date of the instant application. Applicants note that a reference cited under 35 U. S. C. § 102(e) may be removed by antedating the reference showing Applicants' prior invention, as provided in C. F. R. § 1.131. This procedure is discussed in MPEP 2136.05.

As discussed during the recent Examiner Interview, Applicants new representative has only recently assumed responsibility for this matter, and as such, have begun obtaining the necessary evidence for antedating the reference. Owing to Assignment of the application, a restructuring of the present corporate Assignee of record in the present case, and the departure of some of the named co-inventors of the application from the successor , Applicants appreciate the patience of the Examiner in providing the required submission under C. F. R. § 1.131.

2.12 THE REJECTION OF CLAIMS 3-7, 13-17, AND 23-27 UNDER 35 U. S. C. § 103(A) IS MOOT FOLLOWING A SUBMISSION UNDER 37 C. F. R. § 1.131 TO REMOVE RIPAMONTI AS PRIOR ART.

Re: Item 14 of the Action:

Claims 3-7, 13-17, and 23-27 were rejected under 35 U. S. C. § 103(a) as allegedly being legally obvious over Ripamonti *et al.* (U.S. Pat. Appl. Publ. No. 2003/1014977).